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ORIGINAL ARTICLE

Effect of triphenylphosphonium moiety on spatial structure and biointeractions of stereochemical variants of YRFK motif

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Abstract

Chemical modification of therapeutic peptides is an important approach to improving their physicochemical and pharmacokinetic properties. The triphenylphosphonium (TPP) cation has proved to be a powerful modifier; however, its effects on peptide structure and activity remain uncharacterized. In this study, cytoprotective tetrapeptides based on the YRFK opioid motif with L- or D-Arg residues were linked to (triphenylphosphonio)carboxylic acids with ethylene and pentylene spacers (TPP-3 and TPP-6 groups, respectively). The three-dimensional structure of the oligopeptides was analyzed by NMR spectroscopy, computational methods and circular dichroism (CD). A more compact and bent structure with segregated aromatic groups was revealed for the D-arginine-containing tetrapeptide and its TPP-6 derivative. The TPP moiety caused structure-organizing effect on the tetrapeptides, resulting in transition from random coil to β-sheet structures, and decreased the peptide backbone flexibility up to ten times. The TPP-3-modified oligopeptide with the lowest RMSD value (ca. 0.05 Å) was characterized by intrapeptide hydrophobic interactions between the TPP and side groups of Tyr and Phe residues accompanied by strong CD induction. The TPP-6-modified oligopeptides showed enhanced ability to form intermolecular associates and disturb liposomal membranes. The relationship between the spatial structure of the oligopeptides and some of their biologically relevant interactions were additionally revealed and are discussed.

Keywords Cationic–aromatic oligopeptides · YRFK motif · Triphenylphosphonium derivatives · NMR spectroscopy · Three-dimensional structure · Biointeractions

Introduction

Oligopeptides are an important object of biomedical research. They are being intensively investigated as bioactive molecules, drug candidates and protein models (Fosgerau and Hoffmann 2015; Shiba 2010; Vlieghe et al. 2010). Oligopeptides are characterized by a potentially high activity and specificity, which could be observed for the simplest di- and tripeptide motifs (Andrea et al. 2005; Ung and Winkler 2011). However, most bioactive peptides are characterized by rapid enzymatic degradation and low cellular and tissue availability which restrict their biomedical application (Shiba 2010).

Chemical conjugation of oligopeptides with artificial compounds, including amino acid analogues, is an established way of increasing stability and improving pharmacokinetic properties of oligopeptides without substantial disruption of their natural structure and functions. For this purpose, terminal and/or side group modification of peptides

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